CONGENITAL IL-12R1B RECEPTOR DEFICIENCY AND THROMBOPHILIA IN A GIRL HOMOZYGOUS FOR AN *IL12RB1* MUTATION AND COMPOUND HETEROZYGOUS FOR *MTFHR* MUTATIONS: A CASE REPORT AND LITERATURE REVIEW

H. H. Akar^{1,*}, M. Kose², O. Ceylan³, T. Patiroglu¹, J. Bustamante^{4,5}, J. L. Casanova^{4,6}, B. N. Akyildiz⁷ and S. Doganay⁸

¹ Department of Pediatric Immunology, Medical Faculty, Erciyes University, Kayseri, Turkey

² Department of Pediatric Pulmonology, Medical Faculty, Erciyes University, Kayseri, Turkey

³ Department of Pediatric Infectious Diseases, Medical Faculty, Erciyes University, Kayseri, Turkey

⁴ Laboratory of Human Genetics of Infectious Diseases, Necker Branch, Institut National de la Santé et de la Recherche Médicale, U980, University Paris Descartes, Necker Medical School, Foundation Imagine, Paris, France

⁵ Center for Study of Primary Immunodeficiencies, AP-HP, Necker Hospital, Paris, France

⁶ St. Giles Laboratory of Human Genetics of Infectious Diseases, Rockefeller Branch, The Rockefeller University, New York, NY, USA

⁷ Department of Pediatric Intensive Care Unit, Medical Faculty, Erciyes University, Kayseri, Turkey

⁸ Department of Pediatric Radiology, Medical Faculty, Erciyes University, Kayseri, Turkey

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Interleukin-12 (IL-12) plays an important role in the production of interferon gamma from T cells and natural killer cells and is essential for protection against intra-macrophagic pathogens such as *Mycobacterium* and *Salmonella*. Here, we describe a 16-year-old girl with homozygous mutation in exon 12 of the *IL12RB1* gene, which causes complete IL-12Rβ1 deficiency in association with heterozygous mutation (C677T and A1298C) in the methylenetetrahydrofolate reductase gene. She presented with disseminated *Mycobacterium tuberculosis* complex infection, retroperitoneal fungal abscess and also thrombosis in the superior mesenteric–portal vein junction. This is the first case report of a primary immunodeficiency associated with a genetically determined venous thrombosis.

Keywords: IL-12Rβ1 receptor deficiency, retroperitoneal fungal abscess, superior mesenteric–portal vein junction thrombosis, methylenetetrahydrofolate reductase, thrombophilia

Introduction

Cell-mediated immunity, in which interaction between T lymphocytes and macrophages is fundamental, is crucial for host defense against intracellular pathogens such as *Mycobacterium* and *Salmonella* species. In this setting the most important step is activation of macrophages by type 1 cytokines, in particular interferon (IFN)-γ [1]. The human molecular genetic dissection of pediatric tuberculosis (TB) was facilitated from 1996 onward by the dissection of genetic etiologies of the syndrome of Mendelian susceptibility to mycobacterial disease (MSMD), which is characterized by clinical disease caused by weakly virulent mycobacteria, such as BCG-vaccines and environmental mycobacteria (EM; also known as atypical or non-tubercu-

lous mycobacteria), in otherwise healthy children who are normally resistant to most other infectious agents. These patients are also susceptible to *Mycobacterium tuberculosis* (Mtb) [2–3, 5]. The study of patients with MSMD has demonstrated the key role of the IL-12/IFN-γ axis in immunity to mycobacteria in humans [4, 6]. There are as many as 17 genetic etiologies of MSMD. They involve nine genes controlling IFN-γ immunity [5, 6, 9]. The most common etiology is autosomal recessive IL-12Rβ1 deficiency, which represents approximately 40% of all MSMD cases [3, 7]. Here, we describe the first case of IL-12Rβ1 deficiency in a girl who also has thrombosis in superior mesenteric and portal vein junction associated with heterozygous mutation (C677T and A1298C) in the *methylenetetrahydrofolate reductase* (*MTHFR*) gene.

*Corresponding author: H. H. Akar, MD; Department of Pediatric Immunology, School of Medicine, Erciyes University, Kayseri, Turkey, Phone: +90 352 207 66 66/25300, Fax: +90 352 437 58 25, E-mail: himmetakar@gmail.com

Case report

A 16-year-old girl is the first child of healthy parents who are second-degree cousins in Turkey. All three siblings (including the patient) were vaccinated with *Bacillus Calmette–Guerin* (BCG), with no overt adverse effect in the following months. One brother is healthy at 11 years of age. The second brother with a history of pulmonary

Fig. 1. Axial CT image shows right retroperitoneal abscess (long arrow), chronic thrombosis in the main portal vein (thick arrow) and cavernous transformation (short arrow)

Fig. 2. Axial T1-weighted MR image shows nodular enhancement (tuberculoma) in the right pons (arrow)

TB is 5 years old. The patient's parents and oldest brother had negative tuberculin skin test results. The patient's illness began when she was two years old with fever, weakness and a cervical mass with purulent discharge. She had axillary, retroauricular and inguinal lymphadenopathies. She was treated with antituberculosis (anti-TB) drugs four times for tuberculosis lymphadenitis (3 times cervical and 1 axillary). The first anti-TB treatment (isoniazid, pyrazinamide, and rifampicin) was given when she was 10 years old. At the age of 14, she was being treated again with anti-TB drugs (isoniazid, pyrazinamide, and rifampicin) for 6 months in another university hospital. This treatment went on for 6 months. She also experienced retroperitoneal abscess in those years. The etiology was found to be non-typhoidal *Salmonella* from abscess culture. After 6 months of anti-TB treatment, she was admitted to the hospital with productive cough, weakness, fatigue, abdominal pain, and night sweat. Physical examination revealed an anterior cervical 4×3 cm mass with pain and fluctuation, crackles on examination of the respiratory system, and infiltration on chest X-ray. Her weight was below the third percentile but her height was normal. At that time, laboratory test results were normal for counter blood cell (CBC), immunoglobulins (A, G, M, E and subgroup G), lymphocyte subsets and phagotest. *Mycobacterium tuberculosis* complex (MTBC) was cultured from the drained material of cervical mass with BACTEC automated system. Acid-fast bacilli were detected from gastric lavage of the fasting stomach in the morning. Also, acid-fast bacilli were seen in the drained material. Whole blood samples were *in vitro* activated with BCG, BCG plus IL-12 and BCG plus IFN- γ as described previously [4]. IL-12p40 production was increased after stimulation with BCG plus IFN- γ . In contrast, IFN- γ production in response to BCG plus IL-12 was blunted. Mutation analysis revealed a homozygous mutation, R486X, in exon 12 of *IL12RB1*. Biological materials were not available for parents and siblings. After this medical history, physical examination, positive laboratory findings, quartet anti-TB treatment (isoniazid, pyrazinamide, rifampicin, and ethambutol) were resumed. The patient with this treatment was being followed. The patient did not come to polyclinic control for almost one year. At the age of 16, the patient was admitted to the pediatric emergency department with fever, productive cough, abdominal pain, headache, blurred vision, weakness, fatigue, and night sweats. Hepatosplenomegaly, superior mesenteric–portal vein junction thrombosis, and plenty of collateral veins were demonstrated with the ultrasonography of abdomen. The computerized abdominal tomography (CT) showed 4.5×3.5 cm retroperitoneal abscess

(Fig. 1) and multiple lymphadenopathies in addition of ultrasound. The thrombosis was evaluated chronically. The patient was found to be compound heterozygous for the *MTFHR* gene both in C677T and A1298C alleles. Homocysteine, vitamin B12 and folate levels were normal. Enoxaparin was given to the patient for thrombosis. Retroperitoneal abscess was drained by interventional radiologist. *Candida albicans* was cultured from drained material. Fluconazole was added to the patient's treatment. Cranial magnetic resonance imaging (MRI) showed focal nodular enhancing lesion in right posterolateral zone of pons (tuberculosis granuloma?) (Fig. 2) and irregularity and thickening with pathological contrast enhancement in the left middle cerebral artery wall probably due to vascular involvement of TB (Fig. 3). Bilateral pupil edema was seen on fundoscopic examination. Methylprednisolone was started to the patient. *Mycobacterium tuberculosis* Polymerase Chain Reaction (PCR) was found to be positive in the cerebrospinal fluid. Also MTBC was grown in cerebrospinal fluid culture. Second month in the hospitalization, repeated cranial MRI showed enhancement and thickening of basal cisterns consistent with TB meningitis (Fig. 4) and again thickening and enhancement of left middle cerebral artery consistent with TB vasculitis and left thalamic lacunar infarction. The patient experienced sudden unconsciousness at the third month in hospitalization. Cranial MRI revealed acute infarction in both cerebral hemispheres. The patient was interned to the pediatric intensive care unit. The patient died almost four months after the hospitalization in pediatric intensive care unit.

Discussion

Here, we report a 16-year-old girl with disseminated MTBC and superior mesenteric–portal venous junction thrombosis. The diagnosis was based on both clinical and genetic features. In our patient, MTBC was cultured from cerebrospinal fluid and drained cervical mass. *C. albicans* was cultured from retroperitoneal abscess material. Non-typhoidal *Salmonella* was cultured in retroperitoneal abscess. These three microbes, *M. tuberculosis*, *Salmonella* and *C. albicans* have been reported in patients with MSMD, including in particular patients with IL-12R β 1 and IL-12p40 deficiencies [8–10]. She had a complete IL-12R β 1 deficiency caused by a homozygous mutation in the *IL12RB1*. IL-12 and IL-23 are produced by macrophages and dendritic cells, binding to their receptors consisting of IL-12R β 1 and IL-12R β 2 that are expressed on natural killer

Fig. 3. Axial T1-weighted MR image shows thickening and enhancement in the left middle cerebral artery wall (arrow)

Fig. 4. Axial T1-weighted MR image shows pathologic thickening and enhancement of basal cisterns (arrow)

cells and T lymphocytes. This stimulation causes IFN- γ production. IFN- γ binds to IFN- γ receptor and leads to phosphorylation of a signal transducer and activator of transcription type 1 (STAT-1). Defects in any pathway of the IL-12/IFN- γ axis cause susceptibility to mycobacteria or other infectious pathogens in humans [7, 8]. Impaired IL-23-dependent expansion of IL-17 T cells also probably account for candidiasis in such patients [11–13].

Another clinical manifestation in this patient was superior mesenteric–portal venous junction thrombosis, probably due to constitutive thrombophilia. To our knowledge, this clinical manifestation was never reported in IL-12R β 1 deficiency. Congenital thrombophilia includes deficiencies of antithrombin III, protein C and protein S, and the factor V Leiden mutation, the prothrombin gene variant and bi-allelic mutations in the *MTHFR* [14]. Congenital thrombophilias are responsible from almost 35% percent of the etiology of intraabdominal vein thrombosis events [15]. Splenic and mesenteric venous thrombosis in an adult, who has compound heterozygous for the *MTFHR* C677T and A1298C alleles, was reported by Gürsoy et al. [16] from Turkey. Also, Jurcuț et al. [17] reported a patient with recurrent deep thrombosis related to hyperhomocysteinemia, and compound heterozygosity for the C677T and A1298C mutations. A study suggested that mutations in *MTHFR* gene for allele C677T and A1298C have a tendency to associate with coronary artery disease, in both homozygous and heterozygous carriers even when blood homocysteine levels were not elevated [18]. The patient reported here, whose homocysteine level was not elevated, was heterozygous for both C677T and A1298C alleles of *MTHFR* gene.

In conclusion, the present case report neatly emphasizes the importance of considering multiple genetic disorders in individual patients with a complex phenotype. Ehlayel et al. [19] had previously reported the occurrence of IL-12R β 1 deficiency and Ataxia-Telangiectasia. Another group had also reported Wiskott–Aldrich syndrome in a family with Fanconi anemia [20]. Congenital thrombophilia should be considered in immunodeficient patients with unexplained idiopathic venous thrombosis, as illustrated in the patient reported here, who suffered from both IL-12R β 1 deficiency and thrombophilia.

Conflict of interest

The authors declare that they have no conflict of interest.

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